



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### Pulmonary Cowpox in Cats: Five Cases

**Citation for published version:**

McInerney, J, Papasouliotis, K, Simpson, K, English, K, Cook, S, Milne, E & Gunn-Moore, D 2016, 'Pulmonary Cowpox in Cats: Five Cases', *Journal of Feline Medicine and Surgery*, vol. 18, no. 6, pp. 518-525. <https://doi.org/10.1177/1098612X15583344>

**Digital Object Identifier (DOI):**

[10.1177/1098612X15583344](https://doi.org/10.1177/1098612X15583344)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Journal of Feline Medicine and Surgery

**Publisher Rights Statement:**

This is the author's final accepted manuscript that has been through the peer-review process. Once the article has been accepted for publication, the author may post this version of the paper into the institutional repository without any restrictions.  
<http://www.sagepub.com/oa/funding.cp>

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



## Pulmonary Cowpox in Cats: Five Cases

McInerney, J.<sup>ψ</sup>, Papasouliotis, K.<sup>¥</sup>, Simpson, K.<sup>º</sup>, English, K.<sup>~</sup>, Cook, S.<sup>¢</sup>, Milne, E.<sup>†</sup>, Gunn-Moore, D.A.<sup>†</sup>

<sup>ψ</sup>Corresponding author; Small Animal Hospital, University of Glasgow, 464 Bearsden Road, Glasgow, G61 1QH, Scotland: [jenniemcinerney@live.com](mailto:jenniemcinerney@live.com) 07795356134

<sup>¥</sup> University of Bristol, School of Veterinary Sciences, Langford Veterinary Services Diagnostic Laboratories, Langford House, Bristol, BS40 5DU, UK

<sup>º</sup> Orange House, Jitsin, Koh Tao, 84280, Thailand

<sup>~</sup> Department of Pathology and Pathogen Biology, The Royal Veterinary College, North Mymms, Hatfield, Hertfordshire, AL9 7TA, UK

<sup>¢</sup> Clinical Science and Services, The Royal Veterinary College, North Mymms, Hatfield, Hertfordshire, AL9 7TA, UK

<sup>†</sup> Joint last authors; Royal (Dick) School of Veterinary Studies and The Roslin Institute, The University of Edinburgh, Easter Bush Campus, Roslin, EH25 9RG, Scotland

### **Key words**

Cowpox virus; cats; pneumonia; zoonotic risk

## Abstract

*Case series summary:* This case series documents five cases of pneumonia (with pleural effusion in three cases) caused by cowpox virus (CPxV) in domestic cats. Predisposition to pneumonia may have resulted from mixed infections in two cases (feline herpes virus and *Bordetella bronchiseptica* in one cat, and *Mycoplasma* spp. in the other).

*Relevance and novel information:* Diagnosis was not only confirmed by previously described methods of virus isolation from skin lesions, demonstration of pox virions in skin samples using electron microscopy and inclusion bodies in histological preparations, but it is the first report of diagnosis by virus isolation from bronchoalveolar lavage fluid (BALF) or pleural fluid, and the demonstration of inclusion bodies in cytological preparations. This is also the first series to report treatment with interferon omega (IFN- $\omega$ ). Two cats survived, both of which had been treated with IFN- $\omega$ . Since CPxV has a serious zoonotic risk it is an important differential diagnosis of pneumonia in cats.

## Introduction

Cowpox virus (CPxV) belongs to the *Orthopoxviridae* genera, and is endemic in northern Europe and western areas of the former Soviet Union.<sup>1</sup> Although called cowpox, it rarely infects cattle; disease is most common in domestic cats, with over 400 cases having been reported.<sup>2-6</sup> However, infections are commonly missed by owners and veterinarians, so prevalence may be higher than documented.<sup>5</sup>

The reservoir hosts are believed to be bank voles (*Myodes glareolus*), field voles (*Microtus agrestis*) and wood mice (*Apodemus sylvaticus*) as they have the highest prevalence of antibodies to CPxV.<sup>7,8</sup> Cats are exposed to CPxV when hunting,<sup>9</sup> so there are more feline CPxV-infections in the autumn when the host populations are at their most numerous.<sup>2</sup>

The outcome of feline infection depends on CPxV strain, route and site of infection, dose of inoculated virus,<sup>5</sup> and presence of systemic immunosuppression, e.g. concurrent feline immunodeficiency virus (FIV) or feline leukaemia virus (FeLV) infection,<sup>2,10</sup> or the administration of systemic glucocorticoids.<sup>2</sup> CPxV infection most commonly presents as focal cutaneous lesions, which heal spontaneously, with no systemic signs. Concurrent oral lesions occur in approximately 20% of cats,<sup>11</sup> and occasional reports document severe, necrotising, sometimes fatal, cutaneous lesions.<sup>12</sup> Fatal necrotising pneumonia has been described in a small number of papers,<sup>13-15</sup> but to the authors' knowledge there has been only one case of CPxV-associated pneumonia that survived.<sup>16</sup>

Although zoonotic transmission is rare, it is reported<sup>3, 15, 17, 18</sup> and can be potentially fatal.<sup>19</sup> It is therefore important that CPxV infection be considered as a differential diagnosis in cases of pneumonia and/or dermatitis in cats.

This case series documents five cases of CPxV-pneumonia in domestic cats, which were all referred for respiratory signs rather than cutaneous lesions. Two cases recovered; both received immunomodulatory therapy. Three cases died, two of which also received immunomodulatory therapy.

## **Materials and methods**

Cytological examinations of lung fine needle aspirates (FNA), BALF and pleural fluid from Cases 1-4 were carried out on direct smears and fluid samples concentrated by cytocentrifugation (Cytospin 3(R), Thermo Fisher Scientific, Loughborough, UK) followed by standard staining with May-Grünwald Giemsa (MGG). Cytological examinations of lung FNA and BALF from Case 5 were carried out following staining with modified Wrights (Hematek, Siemens, USA) stain.

Biopsy and post mortem tissue samples were fixed in 10% phosphate-buffered formalin (pH 7.4), embedded in paraffin wax, and sections (4µm) stained with haematoxylin and eosin (HE) using routine methods.

## **Case Details**

### **Case 1:**

A 4-year-old, neutered male Russian Blue cat was referred to the University of Edinburgh (UoE) in October 2002 after five days of inappetence and lethargy. The cat was vaccinated against feline calicivirus (FCV), feline herpes virus (FHV-1) and feline panleukopenia virus (FPV); it was a keen hunter.

The cat was dyspnoeic, with bilaterally harsh lung sounds, and bilateral dullness on thoracic percussion. Multiple, 2-5mm diameter, circumscribed, papular skin lesions were present on the head and neck, which became erythematous on palpation (Fig 1).

Routine haematology and serum biochemistry were unremarkable except for a mature neutrophilia ( $43.35 \times 10^9/l$ ; reference interval (RI) 7-20) and increased urea (15.75mmol/l; RI 5.71-12.85). Serum was negative for FeLV antigen, and FIV and feline coronavirus (FCoV) antibodies. Thoracic radiographs showed consolidation of the right cranial and middle lung lobes and a low volume effusion was also present. Pleural fluid cytology revealed a pyothorax containing mostly non-degenerate neutrophils, with some activated macrophages (occasionally containing phagocytosed neutrophils), mesothelial cells and a small number of variably-sized lymphocytes. Bacterial culture was negative, including extended culture for *Mycoplasma* spp. Histopathology of the skin lesions revealed extensive necrotising dermatitis with viral inclusions in the epidermis and panniculus. Electron microscopy identified Poxvirus viral particles (Fig 2).

The cat was given recombinant feline interferon omega (rFeIFN- $\omega$ : Virbagen Omega, Virbac, UK: 1MU/kg IV q24 hr); marbofloxacin (Marbocyl, Vetoquinol, UK: 2mg/kg IV q24hr) and clindamycin (Dalacin, Pfizer, UK: 10mg/kg IV q12hr).

When the dyspnoea worsened a median sternotomy and right cranial and middle lung lobectomy was performed. Lung histopathology revealed acute, fibrinous pneumonia with extensive alveolitis; numerous cytoplasmic inclusion bodies and multinucleated giant cells suggested a viral aetiology. Bacterial culture was sterile.

Complications led to euthanasia. Post-mortem examination revealed diffuse, severe pneumonia with many 6-10mm diameter CPxV lesions on the surface of the lungs (Fig 3). Widespread vasculitis, lymphadenopathy and splenic histiocytosis were also present. Lung histopathology revealed areas of pronounced necrosis, with remaining groups of hyperplastic epithelial cells containing eosinophilic, intracytoplasmic inclusions lining bronchi, bronchioles and alveolar septae. Similar inclusions were seen in epidermal and follicular epithelial cells of the skin. Inclusion bodies were consistent with CPxV infection. Electron microscopy of the skin lesions confirmed poxvirus.

#### **Case 2:**

A two-year-old, neutered male, Rag Doll cat was referred to the UoE with acute tachypnoea and coughing in January 2009. The cat was vaccinated against FCV, FHV-1 and FPV, and was an avid hunter. It was tachypnoeic at 66 breaths per minute (bpm), had reduced chest compressibility and squeaks on pulmonary auscultation. A 6mm-diameter, ulcerated skin lesion was present over its left stifle area. Overnight, the cat developed 5-10mm-diameter, erythematous, ulcerated skin lesions with necrotic centres, over its head, neck and thorax (Fig 4). Respiratory rate and effort increased.

Haematology revealed mild neutropenia ( $5.9 \times 10^9/L$ ; RI 7-20) and lymphopenia ( $0.9 \times 10^9/L$ ; RI 1.5-7). Serum biochemistry was unremarkable and serum was negative for FeLV antigen and FIV antibodies. Thoracic radiography revealed consolidation of the right lung and the middle of the left lung (Fig 5a, 5b). Ultrasonography confirmed severe consolidation of the right lung. A small right-sided pleural effusion was evident. Thoracocentesis, bronchoalveolar lavage (BAL) and a FNA of the right lung were performed. Bronchoscopy showed severe hyperaemia of the airway.

Cytology of the lung aspirate revealed acute necrotising pneumonia with clumps of pale basophilic material (presumptive necrotic material), numerous non-degenerate neutrophils and a few lymphocytes and macrophages. Alveolar epithelial cells showed anisocytosis, anisokaryosis and variably basophilic cytoplasm. Cytology of the pleural fluid revealed an exudate with reactive lymphocytes and large granular lymphocytes; it was sterile on bacterial culture. Cytology of BALF revealed numerous neutrophils which were mainly degenerate, ciliated respiratory epithelial cells and occasional goblet cells consistent with acute neutrophilic bronchopneumonia with mucus hypersecretion. It was sterile on routine bacterial culture, and negative for *Mycoplasma* spp.; CPxV was

isolated on extended viral culture. Skin histopathology showed severe necrotising ulcerative dermatitis with intra-cytoplasmic viral inclusion bodies; confirmed as CPxV on virus isolation.

The cat was treated with rFeIFN- $\omega$  (Virbagen Omega, 1MU/kg SC q24 hr); terbutaline (Bricanyl, AstraZeneca, UK: 0.015mg/kg IV q4hr); amoxicillin-clavulanate (Augmentin, GlaxoSmithKline, UK: 20mg/kg, IV q8hr); clindamycin (Dalacin, 11mg/kg IV q12hr) and fluticasone/salmeterol inhaler (Seretide, GlaxoSmithKline, UK: 2 puffs q12hr). Enlargement of skin lesions ceased after 12 hours of treatment. After three days, when the clinical signs were improving, the rFeIFN- $\omega$  and fluticasone/salmeterol were stopped. The cat returned home with a course of amoxicillin-clavulanate (Synulox, Zoetis, UK: 20mg/kg PO q12hr) and clindamycin (Antirobe, Zoetis, UK: 11mg/kg PO q12hr) in case a secondary infection had been missed. Complete recovery was achieved in six weeks.

### **Case 3:**

A two-year-old, neutered female, Domestic Shorthair (DSH) cat was referred to the UoE in September 2009 with a week's history of progressive dyspnoea, wheezing, coughing and anorexia. It was vaccinated against FCV, FHV-1 and FPV, and a known hunter. The cat was markedly dyspnoeic, crackles and wheezes were auscultated over both lung fields and several small, nodular crusting skin lesions were present on the tail.

Haematology and serum biochemistry were unremarkable, and serum was negative for FeLV antigen, and FIV and *Toxoplasma* antibodies. Orthopox virus serology revealed the presence of antibodies (titre 1/128) consistent with acute infection. Poxvirus was cultured from a skin scab. Thoracic radiography revealed consolidation of the left cranial lung lobe; bronchoscopy revealed severe ulcerative tracheitis and bronchitis; BALF was submitted for FHV-1 PCR, FCV and CPxV isolation, routine culture, and extended culture for *Mycoplasma* spp; and oropharyngeal swabs were submitted for FHV-1, FCV and CPxV isolation. Prior to recovery from the anaesthesia, the cat received dexamethasone (Colvasone, Norbrook, UK: 0.07mg/kg IV) to reduce additional inflammation caused by bronchoscopy.

Poxvirus was isolated from the BALF, high levels of FHV-1 DNA was detected in the BALF by PCR indicating active infection and *Bordetella bronchiseptica* was isolated. Poxvirus and FHV-1 were isolated from oropharyngeal swabs. Cytology of the BALF revealed chronic pyogranulomatous bronchopneumonia, with large numbers of non-degenerate neutrophils and macrophages.

The cat was diagnosed with bronchopneumonia caused by CPxV, FHV-1 and *B. bronchiseptica* and mild CPxV-associated dermatitis. It was treated with rFeIFN- $\omega$  (Virbagen Omega, 2.5MU/kg SC q48 hr); marbofloxacin (Marbocyl, 2mg/kg IV q24hr); clindamycin (Dalacin, 10mg/kg IV q12hr) and buprenorphine (Buprecare, Dechra Veterinary products, UK: 0.01mg/kg IV q8hr), and responded well to treatment. Repeat

radiographs three days later demonstrated a marked improvement. The cat was discharged with marbofloxacin (Marbocyl, 2mg/kg PO q24hr) and clindamycin (Antirobe, 10mg/kg PO q12hr) and made a complete recovery over the following three weeks.

#### **Case 4:**

A four-year-old, neutered male DSH cat, who hunted regularly, was referred to the UoE in November 2009 with dyspnoea, coughing and anorexia. The cat was markedly dyspnoeic, with bilaterally increased lung sounds. Thoracic radiography showed consolidation of the entire left lung. Ultrasonography confirmed this, plus a small volume pleural effusion.

The cat was treated with oxygen, marbofloxacin (Marbocyl, 2mg/kg IV q24hr), clindamycin (Dalacin, 10mg/kg IV q12hr), amoxicillin-clavulanate (Augmentin, 20mg/kg IV q8hr), terbutaline (Bricanyl, 0.015mg/kg IV q4hr), dexamethasone (Colvasone, 0.1mg/kg IV q24hr), buprenorphine (Buprecare, 0.01mg/kg IV q8hr) and compound sodium lactate (Hartmann's solution, 5ml/kg/hr IV).

Five, slightly raised, 3-4mm diameter, erythematous skin lesions were then seen over the left thoracic wall. A presumptive diagnosis of CPxV-pneumonia was made and the cat was given rFeIFN- $\omega$  (Virbagen Omega, 1MU/kg IV q24 hr).

Two skin lesions were biopsied for histopathology and CPxV isolation. Cytology of the pleural fluid revealed neutrophilic inflammation. Cytology of a lung FNA was consistent with an acute suppurative pneumonia. However, one large cell (suspected to be a ciliated respiratory epithelial cell) was seen with two to three large, round, amphophilic, inclusions resembling cytoplasmic type A viral inclusions (Fig 6a). This cell, and one other, had elongated structures extending from their cell surface, resembling the actin tails seen in poxvirus infections. In addition, one ciliated respiratory epithelial cell had a circular cluster of small round amphophilic structures resembling a type B inclusion, or possibly *Mycoplasma* spp. organisms. No bacteria were isolated.

The cat deteriorated and was euthanased. Post mortem examination confirmed severe unilateral interstitial pneumonia with bilateral fibrinous pleuritis and severe serosanguineous pleural effusion. Lung histopathology showed severe, diffuse, necrotising pneumonia with fibrinous pleuritis, syncytia and intracytoplasmic eosinophilic inclusion bodies (Fig 6b). These findings were consistent with CPxV-pneumonia. Necrotising tracheitis and ulcerative dermatitis were also confirmed; both with intracytoplasmic inclusion bodies. Skin histopathology revealed severe, epidermal necrosis and ulceration with eosinophilic intracytoplasmic viral inclusions consistent with CPxV infection. *Mycoplasma* spp. was cultured from the pleural fluid and CPxV was cultured from the skin biopsies and pleural fluid.

#### **Case 5:**

A ten-year-old, neutered female, DSH cat was referred to the Emergency and Critical Care department at the Royal Veterinary College with acute onset respiratory distress in September 2014. The cat was vaccinated against FCV, FHV-1 and FPV and had access to outdoors but was not known to hunt.

On presentation she was tachypnoeic but not dyspnoeic, with a respiratory rate of 102 bpm, and harsh lung sounds bilaterally. She was considered cardiovascularly stable. No skin lesions were present.

There were no significant abnormalities on venous blood gas, electrolyte and limited biochemistry analysis. Haematology revealed a moderate neutrophilia of  $19.05 \times 10^9/L$  (RI 2.5-12.5) with a left shift, and mild polychromasia despite haematocrit within reference intervals 40.3% (RI 24-45). Thoracic radiography revealed consolidation of the right caudal, middle and accessory lung lobes. There was no evidence of excess pleural fluid.

The cat was treated with compound sodium lactate (Hartmann's solution, 3ml/kg/hr IV), amoxicillin-clavulanate (Augmentin, 20mg/kg IV q8hr) and oxygen nebulisation. The cat subsequently deteriorated significantly with regards breathing rate and effort and was mechanically ventilated for 24 hours. Anaesthesia for ventilation consisted of propofol (Vetofol, Norbrook, Northern Ireland: 0.2mg/kg/min IV continuous rate infusion (CRI)), fentanyl (Fentadon, Eurovet, Netherlands: 6ug/kg/hr IV CRI) and midazolam (Hypnovel, Roche, UK: 0.25mg/kg/hr IV CRI).

Cytology of the BALF revealed marked neutrophilic inflammation; eosinophils were also present, and epithelial hyperplasia or dysplasia was observed. Bacterial culture of this fluid was negative.

Cytology of a FNA taken from the right caudal lung lobe revealed a predominance of non-degenerate neutrophils with small numbers of lymphocytes and occasional macrophages. Moderate to large numbers of sheets of spindloid to round cells with a small amount of deeply basophilic cytoplasm and central dense nuclei (basal epithelial cells) were present. The remainder of the cells were cuboidal to columnar. Binucleate cells and occasional multinucleate cells were also observed. Occasional epithelial cells were observed containing medium to large, globular, smooth, green/blue appearing or amphophilic inclusions which were suspected to be viral inclusions. Rare cells containing these inclusions had elongated structures consistent with those resembling actin tails as noted in case 4. Moderate to high numbers of goblet cells were also present.

A PCR was carried out on one of the lung aspirate smears and on the BALF and a diagnosis of CPxV induced pneumonia was confirmed from both samples.

The cat was euthanased due to a lack of improvement and financial constraints; a post mortem examination was declined.



## Discussion

To the authors' knowledge this is the first case series of CPxV-induced pneumonia, with or without pleural effusion, in domestic cats. Single cases of fatal necrotising pneumonia have been documented previously in the Netherlands, Germany and the UK.<sup>13-15</sup>

However, there has only been one report of CPxV-pneumonia (with concurrent FHV-1 infection) which recovered.<sup>16</sup>

Cats are thought to become infected with CPxV while hunting wild rodents.<sup>11</sup> Four out of five cats in this series were known rodent hunters and four of the five cases occurred in autumn, consistent with the peak in wild rodent populations.<sup>11</sup>

In cats, the usual route of virus entry appears to be through the skin, resulting in a single primary skin lesion. Poxvirus viraemia may then lead to multiple secondary skin lesions, with fever, inappetence and pneumonia in severe cases.<sup>11</sup> Interestingly, the cats in this paper were all referred for the investigation of respiratory signs, with skin lesions only being found at or after presentation in four cases. A similar presentation was described by Johnson et al.,<sup>16</sup> and skin lesions were never observed in another case of CPxV-pneumonia.<sup>14</sup> The fact that only some cats develop pneumonia may relate to immunosuppression (FeLV, FIV, or renal failure), concurrent bacterial infections, dose of inoculated virus, and/or viral virulence.<sup>2, 10, 20</sup>

Two of our cases (Cases 3 and 4) received glucocorticoids at anti-inflammatory doses. The detrimental effects of glucocorticoids on CPxV infection have been reported previously so immunosuppressive doses are contraindicated.<sup>2</sup> However, in severe pneumonia, anti-inflammatory doses could be beneficial in relieving clinical signs.

Although two of the five cats had concurrent infections, it is unclear whether this predisposed to CPxV-pneumonia and/or exacerbated it. *Mycoplasma* spp. was found in the pleural fluid of Case 4, and this cat died. However, concurrent infection does not always result in severe disease. Cases of CPxV-associated dermatitis with concurrent FPV developed no systemic disease,<sup>21</sup> another case with concurrent canine distemper virus had only skin lesions,<sup>22</sup> and Case 3 in the present report had CPxV-pneumonia with FHV-1 and *B. bronchiseptica* infections and still recovered. Based on this case series, and other reports,<sup>16,21</sup> concurrent infections appear to be relatively common, which highlights the importance of identifying any concurrent infections so that treatment can be tailored to each case.

It is possible that our cats were infected with a virulent strain of CPxV, hence they developed pneumonia. In Germany, several strains have been shown to exist,<sup>23</sup> but, as yet, there are no reports of feline-tropic variants in the UK.<sup>24</sup> While DNA sequencing was not performed in this series, it could be done in future cases to assess the possibility of a strain of CPxV with a higher virulence for cats.

Diagnosis of CPxV-pneumonia can be made by a number of methods. There are no pathognomonic clinical signs, although concurrent skin lesions increase clinical suspicion. Lung consolidation may be seen on thoracic radiographs and/or ultrasound, often with a small pleural effusion,<sup>14,16</sup> as seen in three cats of our study.

Ideally, all suspected CPxV infections should be confirmed by virus isolation.<sup>11</sup> In this series, for the first time, CPxV-associated pneumonia was confirmed by virus isolation from BALF or pleural fluid (Cases 2, 3 and 4); previous studies have isolated virus from lung tissue at necropsy<sup>15</sup> or skin lesions.<sup>16</sup> This is of note as BAL and thoracocentesis are less invasive than lung biopsy. Virus isolation usually takes two to three days,<sup>11</sup> but extended culture for up to ten days is sometimes necessary, as in Case 2.

A description of the cytology of BALF, pleural fluid or pulmonary aspirates does not appear to have been previously reported. It can reveal characteristic intracytoplasmic (type A) inclusion bodies, and in Case 4, occasional inclusion bodies were found in the lung cytology that appeared to be both type A and possibly type B inclusions. Type A, most commonly seen with CPxV, are protein-rich, with small numbers of virus particles at the periphery, while type B are designated “virus factories”, with many virions present. It was also of note that structures resembling actin tails were seen. These are a means to transfer virions between cells, and are typical of poxvirus infection.<sup>25,26</sup>

Histopathology of lung lesions can be useful. Previous reports describe necrotising proliferative bronchointerstitial pneumonia with segmental loss of respiratory epithelium, hypertrophy of type II pneumocytes, a marked infiltrate of neutrophils, macrophages, lymphocytes and plasma cells, fibrin accumulation within airways, and eosinophilic to amphophilic intracytoplasmic type A inclusions in airway epithelial cells with type II pneumocytes.<sup>13,14</sup> Similar findings were present in cases 1 and 4. Histopathology and electron microscopy can help establish a rapid presumptive diagnosis but they do not confirm the identity of the virus.<sup>27</sup>

Serum assays including virus neutralisation, haemagglutination inhibition, complement fixation and ELISA, can detect antibody to Orthopoxvirus,<sup>11</sup> as in Case 3, but a rising titre is required to prove active infection.<sup>27</sup> PCR is also a confirmatory test for CPxV-infection<sup>9</sup> and it can distinguish CPxV from other orthopox viruses.<sup>15</sup> The CPxV strains in this series were not classified by PCR.

Treatment is generally supportive. There are no antiviral drugs licenced to treat CPxV-infection.<sup>28</sup> Historically, most cats with CPxV-pneumonia died despite supportive treatment.<sup>13,14,28</sup> In this series, recombinant feline interferon (rFeIFN- $\omega$ , Virbagen Omega®) was used in four cases. It is an immunomodulatory drug with antiviral properties,<sup>29</sup> and the only interferon licensed in Europe for use in veterinary medicine. It is licensed for the treatment of cats with FeLV and/or FIV-infection (SC injection) and for dogs with canine parvovirus infection (IV injection); it also has *in vitro* antiviral activity against FHV-1, FCV and FCoV.<sup>29,30</sup> While it is only licenced in the UK for cats by SC

injection, it is licenced in Australasia and Japan for the treatment of acute FCV in cats by IV injection. Since it is known to be safe in cats given IV, and our cats with CPxV were seriously ill, we elected to give it by this route so that it could take effect as rapidly as possible.

In this series, four cats received rFelFN- $\omega$  as soon as they were presumptively diagnosed with CPxV-infection, and two recovered. It was considered highly likely that all would have died given the severity of disease, although this cannot be said for certain. Why treatment was only successful in two patients is unknown although the others may have been too severely affected.<sup>29</sup> This case series suggests that rFelFN- $\omega$  may be potentially useful in the treatment for CPxV-associated pneumonia and dermatitis in cats; however, further research is required before this can be confirmed. An optimal treatment regime is not known although the manufacturer recommends 2.5MU/kg every other day IV for three injections when treating acute FCV (data on company file), and 1MU/kg q24hr SC for five consecutive days for the treatment of FeLV infection, to be repeated on day 0, 14, and 60.<sup>31</sup>

Other antiviral drugs could also be considered. The most promising antiviral in cats is famciclovir for the treatment of FHV-1-disease,<sup>29</sup> but its efficacy against CPxV is unknown. Vidarabine has been shown to be effective against poxviruses *in vitro*,<sup>32</sup> and cidofovir has broad-spectrum activity against poxviruses in humans, and CPxV *in vitro*.<sup>33</sup> In cats, cidofovir has been used with good results for the topical treatment of FHV-1 ocular infections,<sup>34</sup> and *in vivo*, it has shown to protect mice from a lethal CPxV respiratory infection.<sup>33</sup> However, more research in cats is needed as this drug has been shown to be nephrotoxic in humans.

Although CPxV-infection is usually mild in healthy humans,<sup>17,18</sup> severe and even fatal systemic disease can occur.<sup>3,15,19</sup> Clinical signs are usually pustular skin lesions on the hands, but the face and eyelids can also be affected.<sup>3</sup> Since cats are thought to be the main source of CPxV for man,<sup>3</sup> cats with possible CPxV-infections should be treated as a zoonotic risk. It is advised that veterinary surgeons handling cats with suspect CPxV-infections should wear gloves and avoid direct contact of lesion material with the eyes, nose and mouth, or with skin wounds.

This case series shows that although an unusual presentation, CPxV-associated pneumonia may be a more common manifestation of CPxV-disease than previously believed. Due to its potential zoonotic risk, CPxV infection must be considered as a differential diagnosis in cats with presenting signs of pneumonia with or without typical cutaneous lesions.

## **Acknowledgments**

The authors would like to thank the referring veterinary surgeons and the clinicians, pathologists and pathology technicians at the Universities of Edinburgh, Bristol and London. Figures 6a and 6b are reproduced from Cowell and Tyler's Diagnostic Cytology and Hematology of the Dog and Cat, 4<sup>th</sup> Edn., Eds. A.C. Valenciano and R.L. Cowell, Elsevier, St. Louis, MO, USA, p287, by kind permission of Elsevier.

#### **Funding**

This study received no external funding.

#### **Conflict of Interest**

The author's declare that there is no conflict of interest.

#### **References**

- 1 Baxby D and Bennett M. **Cowpox virus (Poxviridae)**. In: Webster RG and Granoff A (eds). Encyclopedia of Virology. 2<sup>nd</sup> ed. London: Academic Press 1999, pp 298-304.
- 2 Bennett M, Gaskell CJ, Gaskell RM, et al. **Poxvirus infection in the domestic cat: some clinical and epidemiological observations**. *Vet Rec* 1986; 118: 387-390.
- 3 Baxby D, Bennett M, Getty B. **Human cowpox 1969-93: a review based on 54 cases**. *Br J Dermatol* 1994; 131: 598-607.
- 4 Nowotny N, Fischer OW, Schilcher F, et al. **Poxvirus infection in the domestic cat: Clinical, histopathological, virological and epidemiological studies** [article in German]. *Wien Tierarztl Mschr* 1994; 81: 362-369.
- 5 Essbauer S, Pfeffer M, Meyer H. **Zoonotic poxviruses**. *Vet Microbiol* 2010; 140: 229-236.
- 6 Appl C, von Bomhard W, Hanczaruk M, et al. **Feline cowpoxvirus infections in Germany: clinical and epidemiological aspects** [article in German]. *Berl Munch Tierarztl Wochenschr* 2013; Jan-Feb 126(1-2): 55-61.
- 7 Crouch A, Baxby D, McCracken CM, et al. **Serological evidence for the reservoir hosts of cowpox virus in British wildlife**. *Epidemiol Infect* 1995; 115: 185-191.
- 8 Chantrey J, Meyer H, Baxby D, et al. **Cowpox: reservoir hosts and geographic range**. *Epidemiol Infect* 1999; 122: 455-460.

- 9 Pfeffer M, Pflüghaar S, von Bomhard D, et al. **Retrospective investigation of feline cowpox in Germany.** *Vet Rec* 2002; 150: 50-51.
- 10 Brown A, Bennett M, Gaskell CJ. **Fatal poxvirus infection in association with FIV infection.** *Vet Rec* 1989; 124: 19-20.
- 11 Bennett M, Gaskell CJ, Baxby D, et al. Feline cowpox virus infection. *J Small Anim Pract* 1990; 31: 167-173.
- 12 Godfrey DR, Blundell CJ, Essbauer S, et al. **Unusual presentations of cowpox infection in cats.** *J Small Anim Pract* 2004; 45: 202-205.
- 13 Hinrichs U, van de Poel H, van den Ingh TS, et al. **Necrotizing pneumonia in a cat caused by an Orthopox virus.** *J Comp Pathol* 1999; 121: 191-196.
- 14 Schöniger S, Chan DL, Hollinshead M, et al. **Cowpox virus pneumonia in a domestic cat in Great Britain.** *Vet Rec* 2007; 160: 522-523.
- 15 Schulze C, Alex M, Schirrmeier H, et al. **Generalized Fatal Cowpox virus Infection in a Cat with Transmission to a Human Contact case.** *Zoonoses Public Hlth* 2007; 54: 31-37.
- 16 Johnson MS, Martin M, Stone B, et al. **Survival of a cat with pneumonia due to cowpox virus and feline herpesvirus infection.** *J Small Anim Pract* 2009; 50(9): 498-502.
- 17 Schupp P, Pfeffer M, Meyer H, et al. **Cowpox virus in a 12-year-old boy: rapid identification by an orthopoxvirus-specific polymerase chain reaction.** *Br J Dermatol* 2001; 145: 146 – 150.
- 18 Hawranek T, Tritscher M, Muss WH, et al. **Feline orthopoxvirus infection transmitted from cat to human.** *J Am Acad Dermatol* 2003; 49 (3): 513-518.
- 19 Pfeiff B, Pullmann H, Eis-Hubinger AM, et al. **Lethal animal pox virus infection in an atopic patient simulating variola vera** [article in German]. *Hautarzt* 1991; 42(5):293-7.
- 20 Bennett M, Gaskell RM, Gaskell CJ, et al. **Studies on poxvirus infection in cats.** *Arch Virol* 1989; 104: 19-33.
- 21 Schaudien D, Meyer H, Grunwald D, et al. **Concurrent Infection of a Cat with Cowpox Virus and Feline Parvovirus.** *J Comp Pathol* 2007; 137: 151-154.

- 22 Wiener DJ, Welle MM, Origgi FC. **Cutaneous lesions associated with dual infection caused by canine distemper virus and orthopoxvirus in a domestic cat.** *Vet Dermatol* 2013; 24(5):543-e130.
- 23 Meyer H, Schay C, Mahnel H, et al. **Characterization of orthopoxviruses isolated from man and animals in Germany.** *Arch Virol* 1999; 144(3): 491-501.
- 24 Naidoo J, Baxby D, Bennett M. **Characterization of orthopoxviruses isolated from feline infections in Britain.** *Arch Virol* 1992; 125:261-272.
- 25 Howard AR and Moss B. **Formation of orthopoxvirus cytoplasmic A-type inclusion bodies and embedding of virions are dynamic processes requiring microtubules.** *J Virol* 2012; 86: 5905-5914.
- 26 Pollara JJ, Laster SM, Petty ITD. **Inhibition of poxvirus growth by Terameprocol, a methylated derivative of nordihydroguaiaretic acid.** *Antiviral Res* 2010; 88(3): 287-295.
- 27 Bennett M, Baxby D, Gaskell RM, et al. **The laboratory diagnosis of Orthopoxvirus infection in the domestic cat.** *J Small Anim Pract* 1985; 26: 653-661.
- 28 Sykes JE and Bennett M. **Feline Poxvirus Infections.** In: Sykes J (ed). *Canine and Feline Infectious Diseases*. Missouri: Elsevier, 2013, p 252-255.
- 29 Sykes JE and Papich MG. **Antiviral and immunomodulatory drugs.** In: Sykes J (ed). *Canine and Feline Infectious Diseases*. Missouri: Elsevier, 2013, p 54-65.
- 30 Gutzwiller MER, Brachelente C, Taglinger K, et al. **Feline herpes dermatitis treated with interferon omega.** *Vet Dermatol* 2007; 18(1): 50-54.
- 31 DeMari K, Maynard L, Sanquer A, et al. **Therapeutic effects of recombinant feline interferon-omega on feline leukemia virus (FeLV)-infected and FeLV/feline immunodeficiency virus (FIV)-coinfected symptomatic cats.** *J Vet Intern Med* 2004. Jul-Aug; 18(4): 477-482.
- 32 Greene C and Hartmann K. **Antiviral and Immunomodulatory Chemotherapy.** In: Greene CE (ed). *Infectious Diseases of the Dog and Cat*. 3<sup>rd</sup> ed. Missouri: Elsevier, 2006, p 10-24.
- 33 DeClercq E. **Cidofovir in the treatment of poxvirus infections.** *Antiviral Res* 2002; 55(1): 1-13.
- 34 Fontenelle JP, Powell CC, Veir Jk, et al. **Effect of topical ophthalmic application of cidofovir on experimentally induced primary ocular feline herpesvirus-1 infection in cats.** *Am J Vet Res* 2008. Feb; 69(2): 289-293.

**Figure legends**

**Figure 1.** Case 1, a four-year-old, neutered male Russian Blue cat: this is a photograph of one of the multiple, 2-5mm diameter, circumscribed, papular skin lesions present on the cat's head and neck. *Please note that as this is a zoonotic disease gloves should have been worn.*

**Figure 2.** A scab from Case 1 was found to have viral inclusions in the epidermis and panniculus on histopathological examination, and this image shows poxvirus viral particles as seen by electron microscopy.

**Figure 3.** This image of Case 1, taken *post-mortem*, reveals diffuse, severe pneumonia with many 6-10mm diameter poxvirus lesions on the surface of the lungs (black arrows). The blue arrow indicates surgical clips following lobectomy.

**Figure 4.** Case 2, a two-year-old, neutered male, Rag Doll cat: this photograph shows some of the many 5-10mm-diameter erythematous, ulcerated skin lesions with necrotic centres that developed overnight on the cat's head, neck and thorax. This picture shows the left side of the cat's neck, which has been shaved and an oesophageal feeding tube placed, although not yet sutured to the skin.

**Figure 5a and b.** Case 2: 5a) Dorsoventral thoracic radiograph showing complete consolidation of the right lung and partial consolidation of the middle of the left lung. A small volume right-sided pleural effusion is also present. 5b) Lateral thoracic radiograph showing patchy diffuse, mainly interstitial changes. An oesophageal feeding tube can be seen in place.

**Figure 6a and b.** Case 4, a four-year-old, neutered male, Domestic Shorthaired cat: 6a) Cytology of a fine needle aspirate of lung revealed changes consistent with acute suppurative pneumonia with a large ciliated respiratory epithelial cell containing several type A poxvirus inclusions (arrow). Two normal ciliated cells are also present. May Grünwald Giemsa x1000. 6b) The same cat as above. Lung histopathology showing changes consistent with necrotising pneumonia with fibrinous and intracytoplasmic eosinophilic inclusion bodies (arrows). Haematoxylin and eosin x400.